TABLE 4
THROMBOCYTOPENIA AND PLATELET TRANSFUSIONS[a]

	Placebo (n=696)	Bolus + Infusion (n=708)
	Number of Patients (%)	
Decrease of platelets to <50,000 cells/μL[a]	5 (0.7)	11 (1.6)
Decrease of platelets to <100,000 cells/μL[a]	24 (3.4)	37 (5.2)
Required platelet transfusions[b]	18 (2.6)	39 (5.5)

[a] Platelet count of <50,000 cells/μL are also included in the category of patients with a platelet count of <100,000 cells/μL.
[b] Patients receiving platelet transfusions for thrombocytopenia or any other reason.

TABLE 5
ADVERSE EVENTS AMONG TREATED PATIENTS IN THE EPIC TRIAL

	Placebo (n=681)	Bolus + Infusion (n=678)
	Number of Patients (%)	
System	82 (12.0)	143 (21.1)
	20 (2.9)	35 (5.2)
System	109 (16.0)	125 (18.4)
	61 (9.0)	77 (11.4)
phatic System	3 (0.4)	8 (1.2)
	1 (0.1)	7 (1.0)
	2 (0.3)	7 (1.0)
	0 (0.0)	4 (0.6)
em	2 (0.2)	9 (1.3)
sion/Pleurisy	3 (0.4)	7 (1.0)
	8 (2.6)	23 (3.4)
	3 (0.4)	11 (1.6)
	1 (0.1)	3 (0.7)

...rily the extremities

...ailed PTCAs, the continuous infusion of ...d be stopped because there is no evidence ...icacy in that setting.

...ous bleeding that cannot be controlled by ...ximab and heparin should be discontinued

...PRECAUTIONS: Restoration of Platelet

...mmended dosage of Abciximab is an intra- ...0 mg/kg administered 10–60 minutes be- ...PTCA followed by a continuous intravenous ...μg/min for twelve (12) hours.

...administration

...products should be inspected visually for ...er prior to administration. Preparations ...containing visibly opaque particles should

...r reactions should be anticipated when- ...ations such as Abciximab are adminis- ...rine, dopamine, theophylline, antihista- ...steroids should be available for immedi- ...ome of an allergic reaction or anaphylaxis ...ation should be stopped and appropriate ...

...teral drug products, aseptic procedures ...during the administration of Abciximab. ...ssary amount of Abciximab (2 mg/mL) ...ion through a sterile, non-pyrogenic, ...r 0.2 or 0.22 μm filter (Millipore ...uivalent) into a syringe. The bolus ...ministered 10–60 minutes before the proce- ...

... of Abciximab for the continuous infu- ...ile, non-pyrogenic, low protein-binding ...er (Millipore SLGVO25LS or equivalent) ...ject into 250 mL of sterile 0.9% saline or ...fusion at a rate of 17 mL/hour (10 μg/ ...) via a continuous infusion pump equipped ...ile, non-pyrogenic, low protein-binding ...(Abbott #4524 or equivalent). Discard ...h at the end of the 12-hour infusion. ...be administered in a separate intrave- ...medication should be added to the infu- ...

...have been observed with glass bottles ...tic bags and administration sets.

...2 mg/mL is supplied in 5 mL vials ...00-0002-7140-01).

Vials should be stored at 2 to 8°C (36 to 46°F). Do not freeze. Do not shake. Do not use beyond the expiration date. Discard any unused portion left in the vial.

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FOOTNOTE

Ryan et al., 1988[7]
Classification of coronary lesions according to ACC/AHA criteria is summarized as follows:

Type A Lesions (high success, >85%; low risk)
- Discrete (<10 mm length)
- Concentric
- Readily accessible
- Nonangulated segment, <45°
- Smooth contour
- Little or no calcification

Type B Lesions (moderate success, 60 to 85%; moderate risk)
- Tubular (10 to 20 mm length)
- Eccentric
- Moderate tortuosity of proximal segment
- Moderately angulated segment >45°, <90°
- Irregular contour
- Moderate to heavy calcification
- Total occlusions <3 months old
- Ostial in location
- Bifurcation lesions requiring double guide wires
- Some thrombus present

Type C Lesions (low success, <60%; high risk)
- Diffuse (>2 cm length)
- Excessive tortuosity of proximal segment
- Extremely angulated segments >90°
- Total occlusion >3 months old
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions

Manufactured by:
Centocor B.V.
Leiden, The Netherlands
U.S. License Number: 1178

Distributed by:
Eli Lilly and Company
Indianapolis, IN 46285 [REV.00]

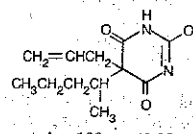
Shown in Product Identification Guide, page 322

SECONAL® SODIUM ©

[sĕk'ō-năl sō'dē-ŭm]
(secobarbital sodium)
Capsules, USP
WARNING: MAY BE HABIT-FORMING

DESCRIPTION

The barbiturates are nonselective central nervous system (CNS) depressants that are primarily used as sedative-hypnotics. In subhypnotic doses, they are also used as anticonvulsants. The barbiturates and their sodium salts are subject to control under the Federal Controlled Substances Act. Seconal® Sodium (Secobarbital Sodium Capsules, USP) is a barbituric acid derivative and occurs as a white, odorless, bitter powder that is very soluble in water, soluble in alcohol, and practically insoluble in ether. Chemically, the drug is sodium 5-allyl-5-(1-methylbutyl)barbiturate, with the empirical formula $C_{12}H_{17}N_2NaO_3$. Its molecular weight is 260.27. The structural formula is as follows:



Each Pulvule® contains 100 mg (0.38 mmol) of secobarbital sodium. It also contains cornstarch, D & C Yellow No. 10, F D & C Red No. 3, gelatin, magnesium stearate, silicone, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Barbiturates are capable of producing all levels of CNS mood alteration, from excitation to mild sedation, hypnosis, and deep coma. Overdosage can produce death. In high enough therapeutic doses, barbiturates induce anesthesia. Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis.

Barbiturate-induced sleep differs from physiologic sleep. Sleep laboratory studies have demonstrated that barbiturates reduce the amount of time spent in the rapid eye movement (REM) phase, or dreaming stage of sleep. Also, Stages III and IV sleep are decreased. Following abrupt cessation of regularly used barbiturates, patients may experience markedly increased dreaming, nightmares, and/or insomnia. Therefore, withdrawal of a single therapeutic dose over 5 or 6 days has been recommended to lessen the REM rebound and disturbed sleep that contribute to drug withdrawal syndrome (for example, decreasing the dose from 3 to 2 doses a day for 1 week).

In studies, secobarbital sodium and pentobarbital sodium have been found to lose most of their effectiveness for both

Continued on next page

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* **Identi-Code® symbol. This product information was prepared in June 1996. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, 800-545-5979.**

Lilly—Cont.

inducing and maintaining sleep by the end of 2 weeks of continued drug administration, even with the use of multiple doses. As with secobarbital sodium and pentobarbital sodium, other barbiturates (including amobarbital) might be expected to lose their effectiveness for inducing and maintaining sleep after about 2 weeks. The short-, intermediate-, and to a lesser degree, long-acting barbiturates have been widely prescribed for treating insomnia. Although the clinical literature abounds with claims that the short-acting barbiturates are superior for producing sleep whereas the intermediate-acting compounds are more effective in maintaining sleep, controlled studies have failed to demonstrate these differential effects. Therefore, as sleep medications, the barbiturates are of limited value beyond short-term use.

Barbiturates have little analgesic action at subanesthetic doses. Rather, in subanesthetic doses, these drugs may increase the reaction to painful stimuli. All barbiturates exhibit anticonvulsant activity in anesthetic doses. However, of the drugs in this class, only phenobarbital, mephobarbital, and metharbital are effective as oral anticonvulsants in subhypnotic doses.

Barbiturates are respiratory depressants, and the degree of depression is dependent on the dose. With hypnotic doses, respiratory depression is similar to that which occurs during physiologic sleep accompanied by a slight decrease in blood pressure and heart rate.

Studies in laboratory animals have shown that barbiturates cause reduction in the tone and contractility of the uterus, ureters, and urinary bladder. However, concentrations of the drugs required to produce this effect in humans are not reached with sedative-hypnotic doses.

Barbiturates do not impair normal hepatic function, but have been shown to induce liver microsomal enzymes, thus increasing and/or altering the metabolism of barbiturates and other drugs (*see* Drug Interactions *under* Precautions).

Pharmacokinetics —Barbiturates are absorbed in varying degrees following oral or parenteral administration. The salts are more rapidly absorbed than are the acids. The rate of absorption is increased if the sodium salt is ingested as a dilute solution or taken on an empty stomach.

Duration of action, which is related to the rate at which the barbiturates are redistributed throughout the body, varies among persons and in the same person from time to time. Seconal Sodium is classified as a short-acting barbiturate when taken orally. Its onset of action is 10 to 15 minutes and its duration of action ranges from 3 to 4 hours.

Barbiturates are weak acids that are absorbed and rapidly distributed to all tissues and fluids, with high concentrations in the brain, liver, and kidneys. Lipid solubility of the barbiturates is the dominant factor in their distribution within the body. The more lipid soluble the barbiturate, the more rapidly it penetrates all tissues of the body. Barbiturates are bound to plasma and tissue proteins to a varying degree, with the degree of binding increasing directly as a function of lipid solubility.

Phenobarbital has the lowest lipid solubility, lowest plasma binding, lowest brain protein binding, the longest delay in onset of activity, and the longest duration of action. At the opposite extreme is secobarbital, which has the highest lipid solubility, highest plasma protein binding, highest brain protein binding, the shortest delay in onset of activity, and the shortest duration of action. The plasma half-life for secobarbital sodium in adults ranges between 15 to 40 hours, with a mean of 28 hours. No data are available for children and newborns.

Barbiturates are metabolized primarily by the hepatic microsomal enzyme system, and the metabolic products are excreted in the urine and, less commonly, in the feces. The excretion of unmetabolized barbiturate is 1 feature that distinguishes the long-acting category from those belonging to other categories, which are almost entirely metabolized. The inactive metabolites of the barbiturates are excreted as conjugates of glucuronic acid.

INDICATIONS AND USAGE

A. Hypnotic, for the short-term treatment of insomnia, since it appears to lose its effectiveness for sleep induction and sleep maintenance after 2 weeks (*see* Clinical Pharmacology).

B. Preanesthetic

CONTRAINDICATIONS

Seconal Sodium is contraindicated in patients who are hypersensitive to barbiturates. It is also contraindicated in patients with a history of manifest or latent porphyria, marked impairment of liver function, or respiratory disease in which dyspnea or obstruction is evident.

WARNINGS

1. *Habit-Forming* —Seconal Sodium may be habit-forming. Tolerance and psychological and physical dependence may occur with continued use (*see* Drug Abuse and Dependence *and* Pharmacokinetics *under* Clinical Pharmacology). Patients who have psychological dependence on barbiturates may increase the dosage or decrease the dosage interval without consulting a physician and subsequently may develop a physical dependence on barbiturates. To minimize the possibility of overdosage or development of dependence, the prescribing and dispensing of sedative-hypnotic barbiturates should be limited to the amount required for the interval until the next appointment. The abrupt cessation after prolonged use in a person who is dependent on the drug may result in withdrawal symptoms, including delirium, convulsions, and possibly death. Barbiturates should be withdrawn gradually from any patient known to be taking excessive doses over long periods of time (*see* Drug Abuse and Dependence).
2. *Acute or Chronic Pain* —Caution should be exercised when barbiturates are administered to patients with acute or chronic pain, because paradoxical excitement could be induced or important symptoms could be masked.
3. *Usage in Pregnancy* —Barbiturates can cause fetal harm when administered to a pregnant woman. Retrospective, case-controlled studies have suggested that there may be a connection between the maternal consumption of barbiturates and a higher than expected incidence of fetal abnormalities. Barbiturates readily cross the placental barrier and are distributed throughout fetal tissues; the highest concentrations are found in the placenta, fetal liver, and brain. Fetal blood levels approach maternal blood levels following parenteral administration.

Withdrawal symptoms occur in infants born to women who receive barbiturates throughout the last trimester of pregnancy (*see* Drug Abuse and Dependence). If Seconal Sodium is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

4. *Synergistic Effects* —The concomitant use of alcohol or other CNS depressants may produce additive CNS-depressant effects.

PRECAUTIONS

General —Barbiturates may be habit-forming. Tolerance and psychological and physical dependence may occur with continuing use (*see* Drug Abuse and Dependence). Barbiturates should be administered with caution, if at all, to patients who are mentally depressed, have suicidal tendencies, or have a history of drug abuse.

Elderly or debilitated patients may react to barbiturates with marked excitement, depression, or confusion. In some persons, especially children, barbiturates repeatedly produce excitement rather than depression.

In patients with hepatic damage, barbiturates should be administered with caution and initially in reduced doses. Barbiturates should not be administered to patients showing the premonitory signs of hepatic coma.

Information for Patients —The following information should be given to patients receiving Seconal Sodium:

1. The use of Seconal Sodium carries with it an associated risk of psychological and/or physical dependence. The patient should be warned against increasing the dose of the drug without consulting a physician.
2. Seconal Sodium may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.
3. Alcohol should not be consumed while taking Seconal Sodium. The concurrent use of Seconal Sodium with other CNS depressants (eg, alcohol, narcotics, tranquilizers, and antihistamines) may result in additional CNS-depressant effects.

Laboratory Tests —Prolonged therapy with barbiturates should be accompanied by periodic laboratory evaluation of organic systems, including hematopoietic, renal, and hepatic systems (*see* General *under* Precautions *and* Adverse Reactions).

Drug Interactions —Most reports of clinically significant drug interactions occurring with the barbiturates have involved phenobarbital. However, the application of these data to other barbiturates appears valid and warrants serial blood level determinations of the relevant drugs when there are multiple therapies.

1. *Anticoagulants* —Phenobarbital lowers the plasma levels of dicumarol and causes a decrease in anticoagulant activity as measured by the prothrombin time. Barbiturates can induce hepatic microsomal enzymes, resulting in increased metabolism and decreased anticoagulant response of oral anticoagulants (eg, warfarin, acenocoumarol, dicumarol, and phenprocoumon). Patients stabilized on anticoagulant therapy may require dosage adjustments if barbiturates are added to or withdrawn from their dosage regimen.
2. *Corticosteroids* —Barbiturates appear to enhance the metabolism of exogenous corticosteroids, probably through the induction of hepatic microsomal enzymes. Patients stabilized on corticosteroid therapy may require dosage adjustments if barbiturates are added to or withdrawn from their dosage regimen.
3. *Griseofulvin* —Phenobarbital appears to interfere with the absorption of orally administered griseofulvin, thus decreasing its blood level. The effect of the ... creased blood levels of griseofulvin on ... sponse has not been established. However, ... preferable to avoid concomitant administration ... drugs.
4. *Doxycycline* —Phenobarbital has been shown ... the half-life of doxycycline for as long as 2 weeks ... biturate therapy is discontinued. This mechanism is probably through the induction ... patic microsomal enzymes that metabolize the ... If barbiturates and doxycycline are administered ... rently, the clinical response to doxycycline ... monitored closely.
5. *Phenytoin, Sodium Valproate, Valproic Acid* —... of barbiturates on the metabolism of phenytoin ... be variable. Some investigators report an ... effect, whereas others report no effect. Because ... of barbiturates on the metabolism of phenytoin ... dictable, phenytoin and barbiturate blood levels ... monitored more frequently if these drugs are ... currently. Sodium valproate and valproic acid ... secobarbital sodium serum levels; therefore, ... sodium blood levels should be monitored closely ... propriate dosage adjustment made as clinically ...
6. *CNS Depressants* —The concomitant use of ... depressants, including other sedatives or hypn... tihistamines, tranquilizers, or alcohol, may ... additive depressant effects.
7. *Monoamine Oxidase Inhibitors (MAOIs)* —MAO ... the effects of barbiturates, probably because ... of the barbiturate is inhibited.
8. *Estradiol, Estrone, Progesterone, and Other Ster... mones* —Pretreatment with or concurrent ad... of phenobarbital may decrease the effect of ... increasing its metabolism. There have been ... tients treated with antiepileptic drugs (eg, phen... who become pregnant while taking oral contra... An alternate contraceptive method might be ... women taking barbiturates.

Carcinogenesis —1. *Animal Data.* Phenobarbital ... is carcinogenic in mice and rats after lifetime ... tion. In mice, it produced benign and malignant ... tumors. In rats, benign liver cell tumors were ... very late in life.

2. *Human Data* —In a 29-year epidemiologic study ... patients who were treated on an anticonvulsant ... that included phenobarbital, results indicated ... than normal incidence of hepatic carcinoma. ... some of these patients had been treated with the ... drug that is known to produce hepatic carcino... this study did not provide sufficient evidence that ... barbital sodium is carcinogenic in humans. A retrospective study of 84 children with brain ... matched to 73 normal controls and 78 cancer con... lignant disease other than brain tumors) sug... association between exposure to barbiturates ... and an increased incidence of brain tumors.

Usage in Pregnancy —1. *Teratogenic Effects. Category D. See* Usage in Pregnancy *under* Warn...
2. *Nonteratogenic Effects.* Reports of infants suffe... long-term barbiturate exposure in utero ... acute withdrawal syndrome of seizures and hyp... ity from birth to a delayed onset of up to 14 da... Abuse and Dependence).

Labor and Delivery —Hypnotic doses of barbitur... appear to impair uterine activity significantly ... Full anesthetic doses of barbiturates decrease ... frequency of uterine contractions. Administration ... tive-hypnotic barbiturates to the mother during ... result in respiratory depression in the newborn. ... infants are particularly susceptible to the depres... of barbiturates. If barbiturates are used during ... delivery, resuscitation equipment should be ... Data are not available to evaluate the effect of ... when forceps delivery or other intervention is ... to determine the effect of barbiturates on the ... development, and functional maturity of the ...

Nursing Mothers —Caution should be exercised ... nal Sodium is administered to a nursing ... small amounts of barbiturates are excreted in ...

ADVERSE REACTIONS

The following adverse reactions and their ... compiled from surveillance of thousands of ... tients who received barbiturates. Because such ... be less aware of some of the milder adverse effects ... rates, the incidence of these reactions may be ... higher in fully ambulatory patients.

More than 1 in 100 Patients

The most common adverse reaction estimated ... rate of 1 to 3 patients per 100 is the following:

Nervous System: Somnolence

Less than 1 in 100 Patients

Adverse reactions estimated to occur at a rate ... in 100 patients are listed below, grouped by ... and by decreasing order of occurrence:

...confusion, hyperkinesia, ...nightmares, nervousness, psychiat... ...ations, insomnia, anxiety, dizziness, ...

...Hypoventilation, apnea
...Bradycardia, hypotension, syncope
...vomiting, constipation
...Headache, injection site reac...
...reactions (angioedema, skin rashes, ...fever, liver damage, megaloblastic ...phenobarbital use

...DEPENDENCE

...Seconal Sodium Capsules are a ...

...rates may be habit-forming; tolerance, ...dence, and physical dependence may ...llowing prolonged use of high doses of ...dministration in excess of 400 mg of ...ximately 90 days is likely to produce ...al dependence. A dosage of 600 to 800 ...gs is sufficient to produce withdrawal ...daily dose for the barbiturate addict is ...As tolerance to barbiturates develops, ...to maintain the same level of intoxica... ...se to a fatal dosage, however, does not ...fold. As this occurs, the margin be... ...sage and fatal dosage becomes smaller. ...ntoxication with barbiturates include ...ed speech, and sustained nystagmus. ...ic intoxication include confusion, poor ...insomnia, and somatic complaints.

...rates dependence are similar to those of ...an individual appears to be intoxicated ...dose that is radically disproportionate to ...el in his or her blood, the use of barbitu... ...ected. The lethal dose of a barbiturate is ...150 ingested.

...barbiturate withdrawal can be severe and ...Mild withdrawal symptoms may appear 8 ...dular dose of a barbiturate. These symp... ...in the following order: anxiety, muscle ...of hands and fingers, progressive weak... ...ortion in visual perception, nausea, vom... ...and orthostatic hypotension. Major with... ...convulsions and delirium) may occur ...ast up to 5 days after abrupt cessation ...ensity of withdrawal symptoms gradually ...d of approximately 15 days. Individuals ...barbiturate abuse and dependence include ...e abusers, as well as other sedative-hyp... ...abusers.

...barbiturates arises from repeated ad... ...continuous basis, generally in amounts ...dose levels. The characteristics of ...barbiturates include the following: (a) a ...to continue taking the drug; (b) a ten... ...dose; (c) a psychic dependence on the ...ed to subjective and individual appre... ...; and (d) a physical dependence on the ...requiring its presence for maintenance of ...resulting in a definite, characteristic, and ...e syndrome when the drug is with...

...barbiturate dependence consists of cautious ...wal of the drug. Barbiturate-dependent ...wn by using a number of withdrawal ...withdrawal takes an extended period. ...substituting a 30-mg dose of phenobar... ...00 mg dose of barbiturate that the pa... ...The total daily amount of phenobarbi... ...in 3 or 4 divided doses, not to exceed ...gns of withdrawal occur on the first ...loading dose of 100 to 200 mg of pheno... ...ered IM in addition to the oral dose. ...phenobarbital, the total daily dose is ...as long as withdrawal is proceeding ...of this regimen involves initiating ...a regular dosage level and decreas... ...10% as tolerated by the patient. ...ally dependent on barbiturates may ...to 10 mg/kg/day. After with... ...ctivity, disturbed sleep, tremors, ...ved, the dosage of phenobarbital ...eased and completely withdrawn

...barbiturates varies considerably. In gen... ...most barbiturates produces serious ...death commonly occurs after 2 to 10 g ...the sedated, therapeutic blood lev... ...between 0.5 to 5 μg/mL; the usual ...from 15 to 40 μg/mL. Barbiturate ...ssed with alcoholism, bromide in... ...neurologic disorders. Potential toler... ...ance must be considered when evaluating significance of dose and plasma concentration.

Signs and Symptoms—Symptoms of oral overdose may occur within 15 minutes and begin with central nervous system depression, underventilation, hypotension, and hypothermia, which may progress to pulmonary edema and death. Hemorrhagic blisters may develop, especially at pressure points.

In extreme overdose, all electrical activity in the brain may cease, in which case a "flat" EEG normally equated with clinical death cannot be accepted as indicative of brain death. This effect is fully reversible unless hypoxic damage occurs. Consideration should be given to the possibility of barbiturate intoxication even in situations that appear to involve trauma.

Complications such as pneumonia, pulmonary edema, cardiac arrhythmias, congestive heart failure, and renal failure may occur. Uremia may increase CNS sensitivity to barbiturates if renal function is impaired. Differential diagnosis should include hypoglycemia, head trauma, cerebrovascular accidents, convulsive states, and diabetic coma.

Treatment—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Diuresis and peritoneal dialysis are of little value; hemodialysis and hemoperfusion enhance drug clearance and should be considered in serious poisoning. If the patient has chronically abused sedatives, withdrawal reactions may be manifest following acute overdose.

DOSAGE AND ADMINISTRATION

Dosages of barbiturates must be individualized with full knowledge of their particular characteristics. Factors of consideration are the patient's age, weight, and condition.

Adults—As a hypnotic, 100 mg at bedtime. Preoperatively, 200 to 300 mg 1 to 2 hours before surgery.

Children—Preoperatively, 2 to 6 mg/kg, with a maximum dosage of 100 mg.

Special patient population—Dosage should be reduced in the elderly or debilitated because these patients may be more sensitive to barbiturates. Dosage should be reduced for patients with impaired renal function or hepatic disease.

HOW SUPPLIED

Pulvules Seconal Sodium (capsules) (orange):
100 mg (No. 240) (Identi-Code* F40)—(100s) NDC 0002-0640-02; (ID† 100) NDC 0002-0640-33

Store at controlled room temperature, 15° to 30°C (59° to 86°F). Dispense in a tight container.

*Identi-Code® (formula identification code, Lilly)
†Identi-Dose (unit dose medication, Lilly)

[072895]

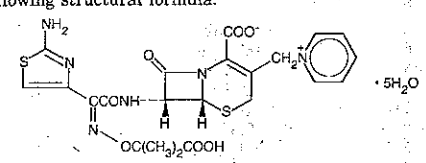
TAZIDIME®

[tă'zĭ-dēm]
(ceftazidime)
for injection
USP

℞

DESCRIPTION

Tazidime® (Ceftazidime, USP) is a semisynthetic, broad-spectrum β-lactam antibiotic for parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl) [(1-carboxy-1-methylethoxy) imino]acetyl]amino]-2-carboxy -8- oxo-5-thia -1-azabicyclo[4.2.0]oct-2-en-3-yl]-methyl]-, hydroxide, inner salt, [6R-[6α,7β(Z)]]. It has the following structural formula:



Tazidime is a sterile, dry powder. Tazidime contains 118 mg (18.5 mmol) sodium carbonate/g of ceftazidime activity. The total sodium content of the mixture is approximately 54 mg (2.34 mEq)/g of ceftazidime activity. Tazidime is sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of anhydrous ceftazidime. Solutions of Tazidime range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly reconstituted solutions usually ranges from 5.0 to 8.0.

CLINICAL PHARMACOLOGY

After intravenous administration of a 500-mg or a 1-g dose of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations were 45 mcg/mL and 90 mcg/mL respectively. Following intravenous infusion of 500-mg, 1-g, and 2-g doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42, 69, and 170 mcg/mL respectively were achieved. The average serum concentrations following intravenous infusion of 500-mg, 1-g, and 2-g doses to these volunteers over an 8-hour period are given in Table 1.

Table 1. Ceftazidime Concentrations in Serum

Ceftazidime Dosage (IV)	Serum Concentrations (mcg/mL)				
	½ h	1 h	2 h	4 h	8 h
500 mg	42	25	12	6	2
1 g	60	39	23	11	3
2 g	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. Following intravenous administration, the half-life was approximately 1.9 hours. Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. Following multiple intravenous doses of 1 g and 2 g every 8 hours for 10 days, there was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function.

Following intramuscular administration of 500-mg and 1-g doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations at approximately 1 hour were 17 mcg/mL and 39 mcg/mL respectively. Serum concentrations remained above 4 mcg/mL for 6 and 8 hours after the intramuscular administration of 500-mg and 1-g doses respectively. The half-life of ceftazidime in these volunteers was approximately 2 hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals who received 2 g intravenously every 8 hours for 5 days. Therefore, a dosage adjustment from the normal recommended dosage is not required for patients with hepatic dysfunction, provided renal function is not impaired.

Approximately 80% to 90% of an intramuscular or intravenous dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. After the intravenous administration of a single 500-mg or 1-g dose, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted 2 to 4 hours after administration, and approximately another 12% of the dose appeared in the urine 4 to 8 hours later. The elimination of ceftazidime by the kidneys resulted in high urinary concentrations.

The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min indicated almost complete elimination of ceftazidime by the renal route. The administration of probenecid prior to administration of ceftazidime had no effect on the elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly prolonged in patients with impaired renal function. Consequently, dosage for such patients must be adjusted (*see* Dosage and Administration).

Therapeutic concentrations of ceftazidime are achieved in tissues and body fluids as listed in Table 2.

[See table at bottom of next page.]

Microbiology—*In vitro* tests demonstrate that ceftazidime is bactericidal, exerting its effect by inhibition of enzymes responsible for cell-wall synthesis. Ceftazidime has *in vitro* activity against a wide range of gram-negative organisms, including strains resistant to gentamicin and other aminoglycosides. In addition, ceftazidime has been shown to be active against gram-positive organisms. It is highly stable to most clinically important β-lactamases, plasmid or chromosomal, that are produced by gram-negative or gram-positive

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* **Identi-Code® symbol. This product information was prepared in June 1996. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, 800-545-5979.**